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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/660,357	BAR-ELI ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	/

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 10/10/03; 11/24/03; 2/23/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-19 are pending and under examination.

Information Disclosure Statement

2. The references listed on the IDS filed 10/10/2003 were not filed with the instant application, however, a copy of these references have been found in related USSN 10/330,357 and have been considered. A signed copy of the IDS filed 10/10/2003 is supplied herein.

Specification

3. The disclosure is objected to because of the following informalities:

The specification is missing a comma after the "5" and a space before the "5" at page 5, line 3.

Appropriate correction is required.

Claim Objections

4. Claims 1 and 10 are objected to because of the following informalities:

Claims 1 and 10 are missing a comma after the "5" and a space before the "5".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-19 are indefinite for reciting "comprising a heavy chain amino acid" in claims 1 and 10. Does the monoclonal antibody comprise a heavy chain amino acid sequence or just a heavy chain amino acid (i.e., a single amino acid form a heavy chain)? Further, it is unclear if the recited sequences (SEQ ID Nos: 1, 5, 9, 13, 17, 21, 25, 29, 33 and 37) are heavy chain sequences or not because a monoclonal antibody comprises both a light and a heavy chain and the claims do not state that the recited sequences are actually heavy chain sequences. Are the recited sequences heavy chain sequences or not?

b. Claim 3 is indefinite for reciting "light chain amino acid having an amino acid sequence". Does a light chain amino acid (i.e., single amino acid) have an amino acid sequence or does the light chain have an amino acid sequence?

c. Claim 3 is indefinite for reciting "further comprises a light chain". Because monoclonal antibodies comprise both heavy and light chains, it is unclear what the

phrase "further comprises a light chain" encompasses. Does the monoclonal antibody comprise an additional light chain sequence? Amending the claim by deleting the term "further" would obviate this rejection.

d. Claim 1 recites the limitation "said cells". There is insufficient antecedent basis for this limitation in the claim. The claim does not recite any cells prior to reciting "said cells".

e. Claims 6, 14 and 19 are indefinite for reciting "the further therapeutic agent". There is insufficient antecedent basis for this limitation in the claim. Base claims 4, 12 and 17 from which claims 6, 14 and 19 depend, respectively, recite "a therapeutic or cytotoxic agent" and not "further therapeutic". Thus, it is unclear if claims 6, 14 and 19 encompass the same or a different therapeutic agent than recited in base claims 4, 12 and 17, respectively. Amending claims 6, 14 and 19 deleting the term "further" would obviate this rejection.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-6, 8-9 and 15-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting melanoma growth/metastasis and lung metastasis in an animal, and a method of inhibiting cell

invasion associated with melanoma, and a method of increasing the survival of an animal having melanoma metastasis or lung metastasis comprising administering a fully human monoclonal antibody conjugated to a therapeutic or cytotoxic agent that binds MUC18, wherein said monoclonal antibody comprises the recited heavy and/or light chain sequences, does not reasonably provide enablement for a method of inhibiting just any tumor growth/tumor metastasis or just any lung tumor and a method of increasing survival of an animal having just any metastatic tumor comprising administering a monoclonal antibody that binds MUC18, wherein said monoclonal antibody comprises the recited heavy and/or light chain sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of inhibiting tumor growth in an animal and a method of increasing survival of an animal having a metastatic tumor comprising

administering a monoclonal antibody that binds MUC18, wherein said monoclonal antibody comprises the recited heavy and/or light chain sequences.

The specification teaches anti-MUC-18 antibodies that inhibit melanoma and lung metastasis in mice and melanoma cell invasion in vitro (see pages 40-44). The specification does not teach the expression of MUC18 in tumors other than melanoma or the use of an antibody that binds MUC18 for inhibiting just any tumor growth/metastasis or a method of increasing the survival of an animal having just any metastatic tumor commensurate in scope with the claims. There is no guidance in the specification as to how to administer the antibodies, the dosages needed, or therapeutic regimens for inhibiting cell proliferation associated with the expression of MUC18. Example 4 of the specification proposes to "determine the *in vivo* effects of anti-MUC18 antibody treatment in human patients with tumors" (see pages 45, lines 27-28). The specification discloses that patients are injected over a certain amount of time with an effective amount of anti-MUC18 antibody and monitoring at periodic times during the treatment to determine whether the tumors progress (i.e., grow and metastasize) (see pages 45-46). Thus, the specification invites the skilled artisan to experiment to determine how to use the claimed antibodies and does not set forth sufficient teachings to allow one skilled in the art to practice inhibiting just any tumor growth/tumor metastasis or just any lung tumor and a method of increasing survival of an animal having just any metastatic tumor with a monoclonal antibody that binds MUC18. There are no working examples to guide or assist the skilled artisan in practicing the claimed method of inhibiting just any tumor growth/tumor metastasis or just any lung tumor and

a method of increasing survival of an animal having just any metastatic tumor with a monoclonal antibody that binds MUC18.

The instant specification provides insufficient guidance or direction to predictably enable one of ordinary skill in the art to use the invention as claimed. Those of skill in the art recognize the unpredictability of treating tumors with antibodies. For example, Jain (Scientific American, 271(1):58-65, July 1994) discloses the art known barriers to the delivery of drugs into solid tumors. These impediments include (1) Non-uniform blood delivery to all areas of the tumor in which some areas of the tumor receive therapeutic agents and other areas of the tumor receive no therapeutic agent at all. (Page 60 col. 3); (2) Increased viscosity of blood in the tumor itself which also hinders drug delivery to the tumor (see paragraph bridging pages 60 and 61); (3) High liquid pressures in the interstitial matrix can retard the delivery of large therapeutic agents, such as antibodies, into tumors (page 61, Col. 1 paragraph 1); (4) Convection is a necessary mechanism by which larger therapeutic molecules such as antibodies, reach target cells which are not directly fed by the vasculature. Convection is not observed in large tumors (defined as more than ½ centimeter in diameter, page 62 col. 1) and convection is necessary for adequate drug delivery of molecules having a molecular weight of more than 5000 (page 61, col. 1 through page 63, col. 3) and (4) Molecules as large as antibodies (i.e., MW=150,000) would require several months to reach a uniform concentration in a tumor that measures 1 centimeter in radius (page 63, col. 2). Further, Dillman [a] (Annals of Internal Medicine, 111:592-603, 1989) summarizes (see abstract) the status of in-vivo use of monoclonal antibodies for treating cancer wherein

despite advances in biotechnology, many major hurdles persist including tumor cell heterogeneity, lack of cytotoxicity, and the development of human anti-mouse antibodies (HAMA). Also, Weiner L. M. (Seminars in Oncology, 26 (4 Suppl 12):41-50, August 1999) provided an overview of monoclonal antibody therapy including some promising activity, however, major obstacles to clinical efficacy still exist extending the unpredictability of this treatment. This includes impaired distribution and delivery of antibody to the tumor site, inadequate trafficking of potential cellular effectors to tumor, antigenic heterogeneity, shed or internalized targets and insufficient target specificity (see page 43). Satyamoorthy et al (Oncogene, 20:4676-4684, 2001, Ids reference 27, filed 10/10/03) teach that the tumorigenic and metastatic phenotype of melanoma cells often correlates with increased expression of cell-cell and cell-matrix adhesion receptors and MUC18 (also known as Mel-CAM, MCAM, CD146) is a cell-cell adhesion receptor highly expressed by melanoma cells, but not normal melanocytes (see abstract). Lehmann et al (Cancer Research, 47:841-845, 1987, Ids reference 19, filed 10/10/03) teaches that the expression of the MUC18 antigen (gp113) is virtually limited to melanoma cells (see page 845 and Tables 2-3).

Furthermore, as disclosed by Dillman [b] (Clinical Oncology, 12(7):1497-1515, 1994) discloses, after reviewing the literature on the use of unconjugated monoclonal antibodies to treat cancer, that "at present, there are no unconjugated monoclonal antibodies that have proven therapeutic benefit in hematologic malignancies or solid tumors." Thus, absent objective evidence to the contrary, it is highly unpredictable that applicant's unconjugated antibody would possess any therapeutic effects.

Satyamoorthy et al (Oncogene, 20:4676-4684, 2001, Ids reference 27, filed 10/10/03) teach that the tumorigenic and metastatic phenotype of melanoma cells often correlates with increased expression of cell-cell and cell-matrix adhesion receptors and MUC18 (also known as Mel-CAM, MCAM, CD146) is a cell-cell adhesion receptor highly expressed by melanoma cells, but not normal melanocytes (see abstract). Lehmann et al (Cancer Research, 47:841-845, 1987, Ids reference 19, filed 10/10/03) teaches that the expression of the MUC18 antigen (gp113) is virtually limited to melanoma cells (see page 845 and Tables 2-3). Thus, absent objective evidence to the contrary, it is highly unpredictable that applicant's antibodies that bind MUC18 would possess any therapeutic effect for just any tumor/metastasis.

No direction or guidance is provided to assist one skilled in the art using a monoclonal antibody that binds MUC18 in a method of inhibiting just any tumor growth/metastasis in an animal and a method of increasing the survival of an animal having just any metastatic tumor, which do not necessarily express MUC18.

In view of the lack of the predictability of the art to which the invention pertains as evidenced by the art of Jain R. K., Dillman [a], Weiner L. M., Dillman J [b], Satyamoorthy et al and Lehmann et al, and the lack of established clinical protocols for effective MUC18 immunotherapy, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably

predictive that the claimed methods are effective for treating just any tumor growth/metastasis, commensurate in scope with the claimed invention.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 10/330,530. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn towards a method of inhibiting tumor growth in an animal, a method of inhibiting cell invasion associated with melanoma and a method of increasing survival of an animal having a metastatic tumor comprising administering a monoclonal antibody that binds MUC18 and has a heavy chain sequence selected from SEQ ID Nos:1, 5, 9, 13, 17, 21, 25, 29, 33 and 37. Instant claim 3 is drawn to a method inhibiting tumor growth in an animal comprising administering a monoclonal antibody that binds MUC18 and has a

heavy chain sequence selected from SEQ ID Nos:1, 5, 9, 13, 17, 21, 25, 29, 33, 37 and a light chain sequence selected from SEQ ID Nos:2, 6, 10, 14, 18, 22, 26, 30, 34, 38 and the claims of Application No. 10/330,530 are drawn to a method of inhibiting cell proliferation associated with the expression of the MUC18 comprising administering a monoclonal antibody having a heavy chain sequence selected from SEQ ID Nos:1, 5, 9, 13, 17, 21, 25, 29, 33 and 37 or a light chain sequence selected from SEQ ID Nos:2, 6, 10, 14, 18, 22, 26, 30, 34 and 38 or both a heavy chain sequence selected from SEQ ID Nos:1, 5, 9, 13, 17, 21, 25, 29, 33, 37 and a light chain sequence selected from SEQ ID Nos:2, 6, 10, 14, 18, 22, 26, 30, 34 and 38, which are identical to the heavy and light chain sequences claimed in the instant application, and wherein said cell is a tumor cell, a melanoma cell and wherein said cell proliferation is tumor metastasis.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-19 are directed to an invention not patentably distinct from claims 1-17 of commonly assigned Application No. 10/330,530. Specifically, see above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned Application No. 10/330,530 discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35

U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER